Remarks

After careful consideration of the outstanding Final Office Action, this application has been re-filed as an RCE application and amended accordingly, and favorable reconsideration on the merits thereof is herewith respectfully requested.

The claims of record prior to the refiling and amendment (claims 9 through 29) correspond identically to the claims presented herein except for independent claim 30 which is a redrafting of independent claim 9. Claim 30 has been amended to more precisely define the anaesthetic control system in order to afford applicants the protection to which they are entitled upon the hopeful withdrawal of the 35 U.S.C. § 112, first paragraph rejection set forth in the Office Action of August 12, 2003. However, since the latter Office Action was made FINAL, independent claim 30 most probably would not have been entered by the Examiner because of the after-final constraints of 37 CFR § 1.116(c) ["showing of good and sufficient reasons why they are necessary and were not earlier presented"]. Accordingly, by the refiling of this application under RCE practice, the entry of the claims is in order and is respectfully requested.

Turning to the only issue of record, the Examiner rejected claims 9 through 29 "under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (See page 2, paragraph 3, first four lines thereof.) The alleged basis for the latter rejection is the Examiner's allegation at page 3, lines 3 through 7 of the last Office Action that Applicant's specification allegedly "fails to provide any

information" on "how the model computing means calculates the actual current value, i.e., the applicant has failed to provide any formulas and/or algorithms that would enable the 'model computing means'." The undersigned has forwarded herewith copies of three pages received from applicant's patent counsel abroad which they downloaded and printed from http://www.anesthesia.at/anesthesiology/tivahome.html. The first page is entitled "TIVA Total Intravenous Anesthesia" and at the bottom there are three parts listed bearing the dates of June, July and October, 1997. "TCI; part 2" are the two other pages forwarded by the German patent counsel and selected phrases and paragraphs have been emphasized by vertical lines in the left-hand margin.

The undersigned visited the latter website/home page and downloaded the entirety thereof, including each of part 1, part 2 and part 3. The entirety of these materials are attached and are available for the Examiner's consideration at the latter-identified website, though the totality of "TCI, part 2" is sufficient for the purposes of this response.

TCI, part 2 first defines Target Control Infusion or TCI as a "computer-assisted administration of propofol for induction and maintenance of general anesthesia." Prior to Target Control Infusion, anaesthesiologist were confronted with the "need for complex calculations" to achieve correct initial administration and subsequent desired concentration levels. However, since at least as early as 1997 such "complex calculations" are no longer necessary and instead pharmacokinetic data (age, gender and weight of patient populations) are "pre-programmed into a pharmacokinetic model, as part of a **computer's program**, which is describing the distribution and elimination of the drug within the body." (Emphasis added.) The

anaesthesiologist need but enter into the computer of the TCI system the target drug concentration "required to induce and also to maintain anaesthesia" of a particular patient. The latter information and the pharmacokinetic model determine the initial loading dose, control the same through the infusion pump of the "TCI-'*Diprifusor*'-system" and, in conjunction with the rate of infusion required to sustain anaesthesia, "controls" the intravenous infusion "completely automatically." As stated in the paragraph immediately following the caption "Control of drug concentration" at the top of page 2, "The pharmacokinetic **program controlling** the drug administration by the infusion pump allows the user to adjust the target drug concentration within the blood or plasma." Thus, the "formulas and/or algorithms" of the TCI system "program" administer the rate of drug infusion on the basis of **desired concentration** whereas the "model computing means" of the invention continuously calculates the concentration within the plasma based on the **delivery rate** while the patient is under anaesthetic treatment. The latter is recited in claim 30, limitation c) followed by "d) control means (17) for generating a control signal dependent upon the present active substance concentration (CN_{actual}) and a desired active substance concentration ($CN_{desired}$)." Thus, by this inventive approach it is possible, by adjusting the delivery rate, to effect actual concentration of the active substance utilizing a "patient model" and well known computer programs and equally well known "formulas and/or algorithms" associated therewith. Accordingly, the enclosed publication clearly evidences **as early as 1997** the existence of a "patient model" capable, **through existing formulas and/or algorithms**, to predict the drug blood or plasma concentration associated with the delivery of a given

amount of drugs so that a person of ordinary skill in the art is enabled to practice the invention of claim 30 and the claims depending therefrom.

In view of the foregoing, the withdrawal of the 35 U.S.C. § 112 rejection of the claims of record, followed by the formal allowance thereof is respectfully requested.

Respectfully submitted,

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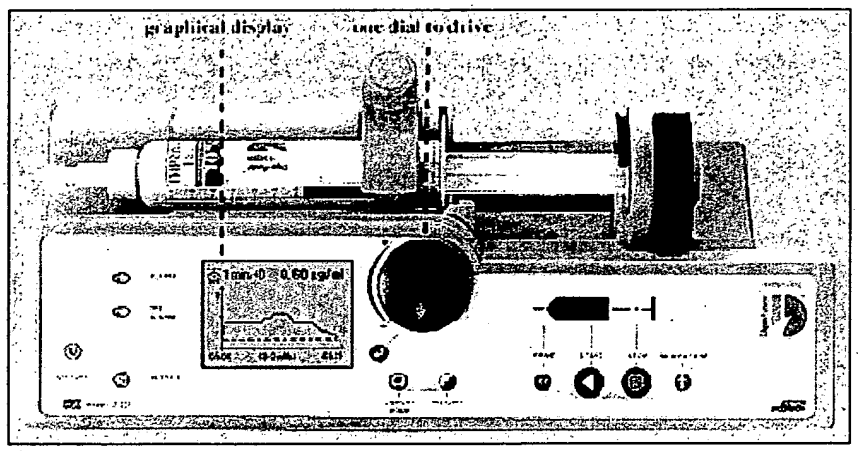
TIVA
Total intravenous Anesthesia

These pages will inform about the **Target Controlled Infusion,** they are maintained by Armin Holas MD, anaesthetist in the Department of Ophthalmology, University of Graz, Austria.

Diprifusor



target controlled infusion
Tiva - target controlled infusion - part 1 - June 1997

- **target controlled infusion**
  Tiva - target controlled infusion - part 2 - July 1997

- **target controlled infusion**
  Tiva - target controlled infusion - part 3 - Oktober 1997

T I V A
Total intravenous
Anesthesia

Target Controlled Infusion - TCI ; part 1

Introduction:

Intravenous anaesthesia and total intravenous anaesthesia (TIVA) as well, are firmly established to an increasing degree in modern anaesthetic techniques in the last ten years. Only the introduction of propofol in the late eighties made this "boost" possible, because in contrast to other hypnotics, like barbiturates and etomidate, propofol is really the best suited intravenous agent for maintenance of anaesthesia.
The characteristics of propofol are well known and have been demonstrated in numerous clinical trials (Reves et al. 1994). Propofol provides a rapid onset of anaesthesia, as shown by its short t 1/2 ke0 (half-time for the concentration to equilibrate between plasma and its effect site, Dyck et al. 1991), and rapid recovery, as shown by its short context-sensitive half-timev (Hughes et al. 1992). In addition, propofol has several advantages over volatile anaesthetics, for example, a very low incidence of postoperative nausea and vomiting (PONV) and it can be used safely in patients susceptible to malignant hyper-thermia. Therefore, propofol is coming up to all requirements, which can be expected from a modern, up-to-date intravenous anaesthetic agent.

Intravenous anaesthesia:
The pharmacokinetic and pharmacodynamic profiles of short-acting intravenous agents, such as propofol, remifentanil, alfentanil or sufentanil, allow rapid titration of drug dose to the required effect in individual patients. This results in stable, satisfactory anaesthetic conditions and a rapid recovery from anaesthesia. The benefits of administering intrave-nous anaesthetics have resulted in an increase in the practice of total intravenous anaesthe-sia (TIVA), in which only intravenous agents are used.

TIVA has several advantages (Sear,1991). Its use:

produces high-quality anaesthetic conditions
avoids the production of fluoride ions associated with some newer volatile agents
avoids distension of air-filled spaces within the patient's body, thus producing optium operating conditions for the surgeon
- avoids postoperative diffusion hypoxaemia

decreases the incidence of PONV
- eliminates occupational exposure to inhalational agents for operating theatre personnel.

Maintenance of Anaesthesia: Intravenous or Inhalational?

Inhalational anaesthetics:
Despite the benefits of TIVA, most general anaesthesia is still maintained using inhalational techniques. The reasons for this have historical roots: Historically, inhalational anaes-thesia developed from intermittent administration using a "Schimmelbusch"-mask to continuous administration using a vaporizer with automatic compensation for changes in pressure and temperature. Inhalational agents may, therefore, be given at precise, control-led concentrations, allowing optimum control of anaesthesia.

The control of inhalational anaesthesia was further improved when the partial pressure of the anaesthestic in expired gas could be measured on-line. The partial pressure of the inhalational anasthetic in blood or plasma, and, more importantly, at the effect site (Central nervous system - CNS), may be estimated from the "endtidal partial pressure", giving some insight into the pharmacokinetic behaviour of the drug involved. The on-line and non-invasive measurement of volatile drug level allows concentration - effect relationships to be determed. This is useful for research purposes and for titrationof the drug to the required effect in the clinical settings.

Intravenous anaesthetics:
Developments in intravenous anaesthesia have lagged behind those in inhalational anaesthesia, though the use of intravenous drugs to produce anaesthesia has a long history. Chloral hydrate was administered intravenously during cataract surgery as early as 1872. Barbiturates were introduced in the 1930s. They were followed by a variety of other induction agents, most of which have now been abandoned. In the last 20 years, etomidate, midazolam and propofol have been introduced as intravenous agents for induction and maintenance of anaesthesia. They are commonly used in combination with opioid analgesics, such as fentanyl and its analogues.

In contrast to the rapid progress seen in the field of inhalational anaesthetics, introduction of new intravenous drugs has not resulted in the rapid development of widely accepted, sophisticated intravenous delivery systems. Today, intravenous agents are still commonly administered by manual bolus on a dose/kg basis. This method of delivery is probably as old-fashioned as administration of volatile agents by the "Schimmelbusch"-mask, which was common practice in 1920 - 1940.

Several new drug delivery systems have been developed for intravenous anaesthesia, however, and introduced during the last 10 years. These are pumps with faster infusion rates and special features, such as "hands-free" bolus

delivery ../congress.htmlction. Despite these sophisticated manually controlled infusion pumps, TIVA is sometimes perceived as being more complicated to perform and difficult to control than inhalational anaesthesia. There is a need for a new intravenous administration system, which is as simple to use as a vaporizer and gives improved control of intravenous anaesthesia compared with current methods. Such an intravenous administration system is now available, and it is called **target-controlled infusion - TCI**.

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Will be continued !

T I V A
Total intravenous
Anesthesia

These pages will inform about the **Target Controlled Infusion**, they are maintained by Armin Holas MD, anaesthetist in the Department of Ophthalmology, University of Graz, Austria.

Target Controlled Infusion - TCI; part 2

Definition:

" Target Controlled Infusion - TCI " is called a computer-assisted administration of propofol for induction and maintenance of general anaesthesia. This new method of intravenous drug administration has been under development for the last 15 years. TCI was published for the first time by ***Schüttler*** and ***Schwilden*** (Bonn, Germany) in **1983** [1] and was improved by ***Kenny*** and ***White*** (Glasgow, Scotland) in **1990** [2]. TCI involves control of an infusion pump, and thus the drug dose administered, by a computer. Until recently, this system was available only for research purposes, but since several months, TCI-devices are available for use in daily clinical practice.

TCI-devices enable the drug concentration in the blood or plasma to be controlled continuously. They also allow administration of intravenous anaesthetics according to their pharmacokinetic profiles without the need for complex calculations by the anaesthetist.

Key pharmacokinetic data are first obtained from clinical measurements in widely different patient populations and include, for example, *age*, *gender* and *weight*. These data are pre-programmed into a pharmacokinetic model, as part of a computer's program, which is describing the distribution and elimination of the drug within the body.

The TCI - system uses these informations to predict the drug blood or plasma concentration associated with the delivery of a given amount of drug. The *target drug concentration* required to induce and also to maintain anaesthesia is entered into the system by the anaesthesiologist. From its pharmacokinetic model, the *TCI-"Diprifusor"-system* determines the initial loading dose needed to achieve the required target concentration and the infusion rate needed to sustain it, and controls hereby the intravenous infusion completely automatically.

Control of drug concentration:

The pharmacokinetic program controlling the drug administration by the infusion pump allows the user to adjust the target drug concentration within the blood or plasma. The drug passes from the blood or plasma to the central nervous system (CNS), to the effect site, where it exerts its activity (**Scott** et al. **1985** [3], **Jacobs** et al. **1993** [4], **Eisenach** et al. **1995** [5]).

In clinical practice, optimum anaesthetic conditions are achieved if the drug concentration in the CNS (= the effect site concentration) is stable, and this depends on stable concentrations of the drug in the blood or plasma. Rapid attainment and maintenance of a constant anaesthetic concentration cannot be achieved accurately using a manually controlled infusion pump, due to the complexity of drug distribution and elimination. This means that the anaesthetist does not know exactly what the blood or effect site concentration is without performing complex calculations . The blood or plasma drug concentration often over- or undershoots the desired value when attempts to stabilize it are made using conventional manual-controlled infusion techniques. This makes it quite difficult to control the depth of anaesthesia.

The pharmacokinetic program of a TCI-device, however, continuously calculates the distribution and elimination of the intravenous anaesthetic agent, and successively adjusts the infusion rate to maintain a predicted blood or plasma drug concentration. One of the main benefits of TCI over manually controlled infusion systems is, therefore, its greater and better control over the drug concentration and the depth of anaesthesia obtained.

Defining Target Controlled Infusion - TCI for anaesthesia:

TCI is **not** a system for the complete computer control of anaesthesia. When using TCI, the anaesthetist adjusts the target blood concentration of the intravenous drug and titrates to clinical effect. A TCI-system is a convenient tool to assist the anaesthetist in adjusting and controlling the depth of anaesthesia.

When applied to anaesthesia, TCI is an infusion system, which allows the anaesthetist to select the target blood concentration required for a particular effect, considering the patient's and operation's needs, then to control depth of anaesthesia by adjusting the requested target concentration during surgery.

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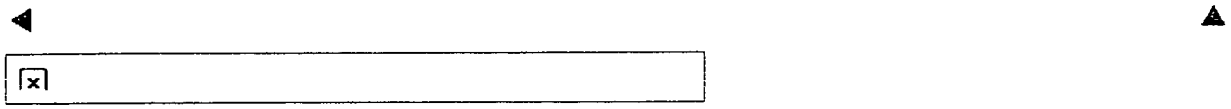
Will be continued !



TIVA
Total intravenous Anesthesia

These pages will inform about the **Target Controlled Infusion**, they are maintained by Armin Holas MD, anaesthetist in the Department of Ophthalmology, University of Graz, Austria.

Target Controlled Infusion - TCI; part 3

Key components of a TCI system The concept of pharmacokinetic models with mathematical equations to describe infusion schedules to provide a target concentration in blood of an intravenous agent originated in 1968 (Kruger-Thiemer 1968). By the early 1980s, *Schüttler et. al.* (Bonn, Germany) had suggested and demonstrated that a computer-controlled infusion pump could deliver complex infusion schedules of intravenous anaesthetic drugs (Schüttler et al. 1983). Subsequently, numerous investigators in Europe and the USA reported experimental systems linking computer software and hardware to the operation of an infusion pump for delivery of intravenous drugs to patients.

The key components of a TCI system

Pharmacokinetics - a validated model with specific parameters for a drug - special algorithm(s) to control infusion rate - "Control unit": i.e. software and microprocessors for above Infusion pump - "Communication systems" between "control unit" and infusion pump - User interFACE for input of patient data and target blood concentration

A TCI system has the following *key components* (figure 2):

Hardware: The hardware needed for TCI comprises: an infusion pump, a computer to control the pump and a safety mechanism to shut the system down in the event of computer failure. This safety mechanism either checks communication between the computer and the pump or involves a separate checking algorithm. The latter calculates the drug concentration based upon the volume delivered by the pump and compares it with the predicted value from the infusion rate control algorithm.

The computer and infusion pump should be integrated and the user interFACE should be as simple as controlling a vaporizer.

Software: Software in the microprocessor incorporates a pharmacokinetic model and a specific set of parameters for the drug to be infused. The microprocessor continuously calculates the variable infusion rates required to achieve a predicted blood concentration. An algorithm controls the operation of the infusion pump so that infusion rates are altered automatically to achieve this blood concentration. The TCI system maintains this concentration until a new target is set by the anaesthetist.

Data specific to the patient: patient-specific data, like *age* and*body weight,* were set by the anaesthetist before anaesthesia is started. Using these informations, the program selects the best set of available pharmocokinetic parameters (25.000!) to predict the drug's behaviour in that specific patient.

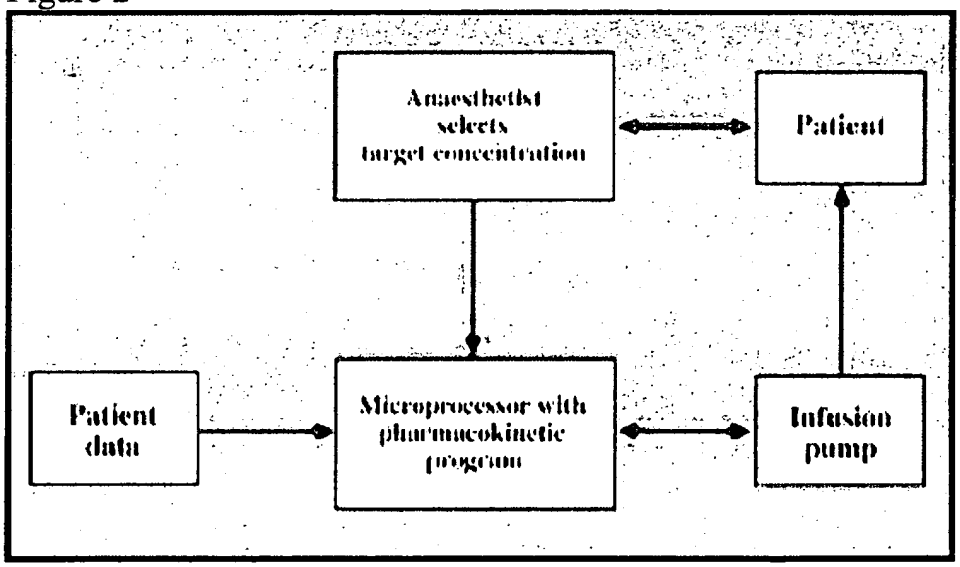
A TCI pump works optimally when:

the computer model controlling the pump works accurately

the pharmocokinetic parameter set used by the model in the computer matches the pharmacokinetic profile of the patient

the pharmacodynamics of the administered drug are well defined.

Figure 2



Main components of a target controlled infusion (TCI) system: The TCI device comprises an infusion pump attached to a computer (microprocessor). The computer's program contains a pharmacokinetic model, describing the elimination and metabolism of the drug within the body, and pharmacokinetic data for widely different patient populations. The target drug concentration and data specific to the patient undergoing surgery, such as age and body weight, are entered into the system by the anaesthetist. From its pharmacokinetic model, the TCI system determines the initial loading dose required to achieve the target concentration and the infusion rate to sustain it, and controls the infusion

automatically.

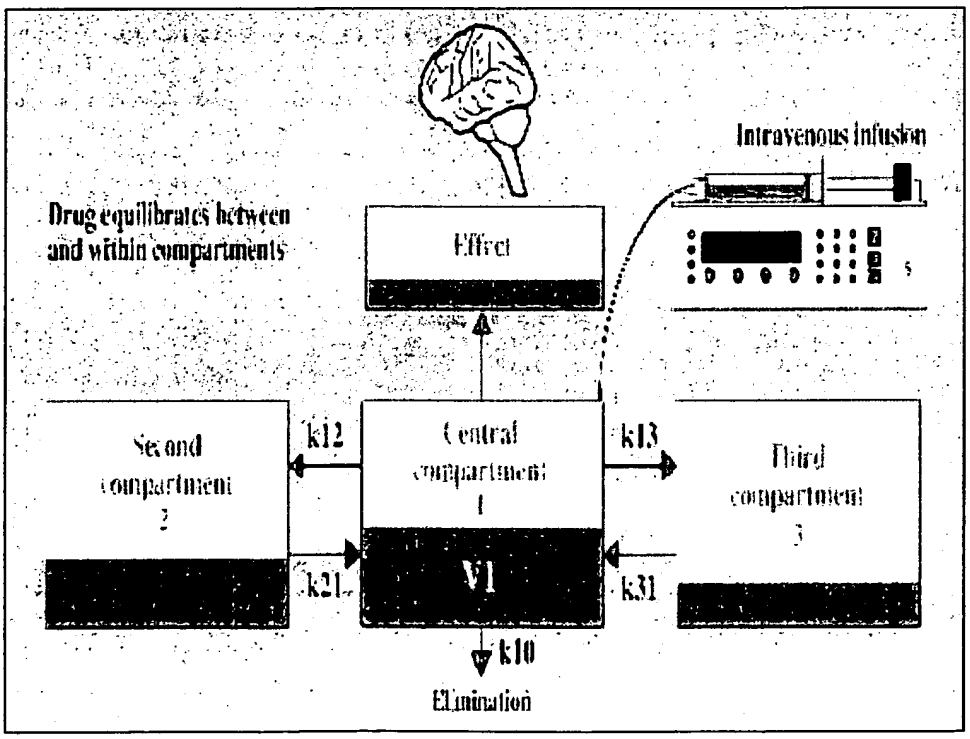
TCI - the pharmacokinetic model

Target Controlled Infusion (TCI) is a logical approach to the development of improved administration techniques for an intravenous anaesthetic agent. TCI is based on an understanding of the agent's pharmacokinetic properties.

The pharmacokinetics of propofol have been evaluated extensively in a variety of disease states and patient groups after either bolus doses or continuous infusions (Bryson et al. 1995, Schüttler 1990, Simons et al. 1988, Gepts et al. 1987). Propofol undergoes rapid and extensive distribution and a rapid metabolic clearance.

After a bolus dose, there is a rapid, initial distribution phase which represents distribution to highly perfused organs such as the brain (effect site). This is followed by a slower, second phase representing redistribution to less well perfused tissues such as muscle. Significant metabolism occurs during this second phase. Recovery from anaesthesia is due to extensive redistribution from the brain and to metabolic clearance.

Figure 3 Pharmacokinetics: open, three-compartment model: schematic representation.



Central compartment represents blood or plasma, the second compartment could represent the highly perfused tissues and the third one the poorly perfused tissues. k_{21}, k_{12}, k_{31} and k_{13} are intercompartmental distribution rate constants i.e. they describe the proportions of drug exchanged between compartments per unit time.

k_{10} is the elimination rate constant from the central compartment.

Open, three-compartment pharmacokinetic model:

The decline of blood concentrations after a bolus dose or termination of infusion can best be described by an open, three-compartment model (Cockshott 1985). Such a model is utilised for the "TCI - Diprifusor" (Coetzee et al. 1995) with a central compartment which represents blood or plasma and two other theoretical compartments (see also figure 3). Based on specific pharmacokinetic parameters of propofol, a computer calculates the changing drug distribution and elimination between and within these three compartments and the amount of drug needed to achieve and maintain the desired propofol blood concentration.

With a manual controlled infusion system, these calculations would not be so easy to manage, because they are too extensive and too complex, as well!

Various models for propofol (Hull 1994) with differing sets of pharmacokinetic parameters have been published by independant research groups. Standardisation and validation of pharmacokinetic parameters are essential for the clinical application of a TCI system.

Three of these models (Marsh et al. 1991, Tackley et al. 1989, Dyck et al. 1992) were examined by ZENECA/England in consultation with principle academic groups. Based on computer simulation and a direct comparison of predicted values with measured values obtained from a study in which the same infusion profile was used in all patients (Servin et al. 1990), the "Marsh-model" (Marsh et al. 1991) was selected for the development of the TCI "Diprifusor". A subsequent comparative study (Coetzee et al. 1995) endorsed the accuracy of the "Marsh" model for TCI using a validated method (Varvel et al. 1992) to compare the accuracy of different models. The pharmacokinetic parameters incorporated in software (© University of Glasgow) used in "Diprifusor" are listed in table 2.

table 2:

Pharmacokinetic parameters* for propofol incorporated in "Diprifusor"-software* (also look at figure 3)

volume of central compartment V_1	228 ml kg^{-1}
Elimination rate constant k_{10}	0,119 min^{-1}

Intercompartmental distribution rate constants	0,114 min^{-1}
k_{12}	
k_{21}	0,055 min^{-1}
k_{13}	0,0419 min^{-1}
k_{31}	0,0033 min^{-1}

* © University of Glasgow

This *open three-compartment model* has the following limitations:

It assumes instant mixing of the drug in the compartments, which does not happen in reality. The model underestimates the drug concentration when its input is high, for example after a bolus or during a fast infusion rate (Wada et al. 1994).

The difference between the predicted and measured blood or plasma concentration is subject to biological variability (Coetzee et al. 1995).

Gross variations in a patient's physiological state may change a drug's pharmacokinetic profile, decreasing the model's predictive value (Flezzani et al. 1987).

Although the model has limitations, pharmacokinetic variability of a drug between individual patients is an everyday issue for anaesthesiologists. *Target Controlled Infusion - TCI* should, therefore, be considered as a helpful tool, similar to a vaporizer in inhalational anaesthesia, in the process of total intravenous anaesthesia (TIVA), which allows to "titrate" the dosage of propofol exactly to the requirements of the individual patient and operation.

An improved *manual* dosing scheme may be developed to achieve a constant drug plasma concentration, with a percentage of error. The difference between the quality of anaesthesia delivered by a well-designed, manual dosing strategy and a *TCI system* is probably not clinically relevant if no change in the target concentration is needed. The objective in anaesthesia, however, whether intravenous or inhalational, is not only to obtain constant drug plasma concentrations, the dose must be adjusted during surgery according to the patient's requirements. Manual infusion schemes are flawed in this respect because the dose-plasma concentration relationship changes with time. The effect

of a bolus or changed infusion rate on the plasma concentration profile given at the beginning of anaesthesia changes as surgery progresses. A *TCI system* does not suffer from this problem because the computer continuously calculates how much drug is within the body respectively in the three compartments, and the concentration achieved is absolutely independent of the duration of infusion.

TCI and pharmacodynamics: interactions with opioids

Several intravenous hypnotics and analgesics are currently used for the induction and maintenance of general anaesthesia. Of all these possible combinations, propofol and alfentanil have the most suitable pharmacokinetic and pharmacodynamic profiles for administration by continuous infusion (Hughes et al. 1992, Gepts et al. 1987, Maitre et al. 1987, Vuyk et al. 1990).

Propofol and opioids in general as well as propofol and alfentanil potentiate one another when given perioperatively. The concentrations of propofol required for loss of conciousness are reduced by 50% in the presence of a plasma alfentanil concentration of 250 ng/ml. On the other side, intraoperatively, with propofol concentrations increasing from 2 to 8 µg/ml, the plasma alfentanil concentration required for adequate anaesthesia is reduced from 250 to 20 ng/ml (Vuyk et al. 1994).

Alfentanil (and other opioids, as well) also affects propofol concentrations at awakening: The higher the residual alfentanil concentration postoperatively, the lower the propofol concentration needs to reduce before the patient wakes up from anaesthesia. The optimum propofol-alfentanil concentration combination producing adequate anaesthesia with the most rapid recovery is 3,5 µg/ml of propofol with 85 ng/ml of alfentanil (Vuyk et al. 1995). Decay curve simulations for these agents following infusions lasting 1- 6 hours showed that this optimum concentration of propofol and alfentanil did not change with the duration of infusion.

A similar behaviour in drug interaction can be seen when propofol is combined with remifentanil, the youngest opioid, which is characterized - in contrast to alfentanil - by an extremely short duration of action and which allows furthermore a rapid and predictable response to alterations in dose (Fragen et al. 1994, Hogue et al. 1995).

Many results in interactive studies with Target Controlled Infusion - TCI and opioids (fentanyl, alfentanil) show a decrease in dose requirements, in target concentrations of propofol for induction and also for maintenance of anaesthesia (Smith et al. 1992, Vuyk et al. 1995, Vuyk et al. 1994) which is confirming again the synergism of different pharmacological components in total intravenous anaesthesia - TIVA (McKay 1991).

Development of Target Controlled Infusion - TCI

The concept of pharmacokinetic models with mathematical equations to describe infusion schedules to provide a target concentration in blood or plasma of an intravenous drug originated in 1968 (Kruger-Thiemer 1968).

In 1983, *Schüttler et al.* (Bonn, Germany) described for the first time the use of a computer to perform the bolus elimination and transfer (BET) infusion scheme with a system called CATIA - "Computer Assisted Total Intravenous Anaesthesia" (Schüttler

et al. 1983). Many other systems followed, for example CCIP - "Computer Controlled Infusion Pump", also including that of *Alvis* (Alvis et al. 1985), who compared the anaesthesia produced with that from a manual dosing scheme. *Shafer's* work with the STANPUMP (Shafer et al. 1988) has been important in the development of TCI. He was the first to propose test criteria for computer-controlled infusion systems.

The first experimental TCI systems were quite bulky and commercial infusion pumps that could be controlled remotely were scarce. *Kenny and White* showed in 1990 that TCI systems could be constructed with smaller computers - even with laptops - and with modern infusion pumps that were simple and reliable to use in daily practice.

Today, there are two computer controlled "Diprifusor" - TCI systems available: First, the "BD Master TCI" by Becton Dickinson and second, the "Graseby 3500" infusion pump by Graseby Medical Limited.

New applications for TCI, such as Target Controlled Infusion of opioids and muscle relaxants or such as for a better postoperative pain control, are currently under investigation worldwide.

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